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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/302,896	04/30/1999	MICHAEL B. CHANCELLOR	2710-4007-US	7603

28089 7590 01/29/2004

HALE AND DORR LLP
300 PARK AVENUE
NEW YORK, NY 10022

EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/302,896	CHANCELLOR ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *196-259* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *196-259* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *05/00* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response and Dr. Michael Chancellor's declaration filed on 01/08/04 has been fully considered.

Claims 1-195 are canceled.

Claims 196-259 are newly filed, which are examined in this office action.

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/08/04 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 196-259 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of repairing urethral muscle tissue injury for the amelioration of stress urinary incontinence by administering autologous muscle-derived primary myoblast cells, does not reasonably provide enablement for a method of repairing or ameliorating damaged or dysfunction of i) urethra muscle tissue, ii) sphincter muscle tissue iii) genitourinary tract tissue or iv) dysfunctional bladder contractility associated with any form of stress urinary incontinence by administering any type of undifferentiated muscle-derived cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

Invention relates to method of treating stress urinary incontinence (ex-vivo gene therapy).

Breadth Of Claims And Guidance Provided in the Specification:

The instant claims are drawn to a method of treating urinary stress incontinence by repairing injured, damaged or dysfunctional i) urethra muscle tissue, ii) sphincter muscle tissue iii) genitourinary tract tissue or iv) bladder tissue by administering an undefined population of undifferentiated muscle derived cells (U-MDC), wherein the U-MDCs are of allogenic or xenogenic origin. The claims are further drawn to the method wherein the U-MDCs are genetically engineered to encode IGF-1 cytokine, any growth factor, IRAP or iNOS polypeptides. In addition the claims are drawn to the method, wherein the U-MDC are subjected to cytokines and growth factors prior to administration of these cells in subject.

At best the instant specification teaches the injection of a genetically engineered **GH8 myoblast cell line** expressing β-galactosidase into the urethral wall of adult female rat with cryo-induced uretheral injury (page 54, example-2, table-1). The specification further teaches injection of the genetically engineered myoblast cell line expressing β-galactosidase and iNOS into the dome of the bladder and into left and

right lateral walls near the dome (page 57, example-3, table-2). The specification concluded that these experiments demonstrated an alteration of bladder and urethral function with cyro-injury model (spec. page 59, line 5). The specification further teaches the injection of myoblasts expression iNOS gene resulted in the release of NO at the site of injection site in penis and bladder but fails to disclose that release of NO resulted in the treatment of urinary stress incontinence (spec. page 79, lines 14-24). Similarly the specification teaches that IGF-1 promotes muscle growth in vitro, but fails to disclose that over expression of IGF-1 would lead to the treatment of urinary stress incontinence (spec. page 83, line 5).

The scope of instant invention as claimed encompasses repairing injured, damaged or dysfunctional i) urethra muscle tissue, ii) sphincter muscle tissue iii) genitourinary tract tissue or iv) bladder tissue in a subject by administering an undefined population of undifferentiated muscle derived cells (U-MDC) to treat stress urinary incontinence. However, the specification as filed fails to disclose what constitutes a population of undifferentiated muscle derived cells, which distinguishes MDC population as claimed from myoblasts. The instant specification fails to disclose that the injection of any and all types of undifferentiated MDCs (allogenic or xenogenic) derived from any and all types of muscles (skeletal or smooth muscles) into the genitourinary tract tissues (as claimed) would lead to the treatment of stress urinary incontinence. The instant specification fails to disclose that injection of genetically engineered undifferentiated MDCs expressing any growth factor, IGF-1 or iNOS would lead to the treatment of stress urinary incontinence. In addition the specification fails to disclose the genetically engineered myoblast cells encoding IRAP would provide immune protection to myoblast cells of xenogenic or allogenic origin.

State Of Art And Predictability:

The instant invention is drawn to a method that requires gene-based therapeutics. The ex-vivo based gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol.

Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case the specification fails to disclose a method of treating stress urinary incontinence by repairing or ameliorating any and all sites in the genitourinary tract tissue (as claimed) by injecting any and all types of undifferentiated muscle derived cells, wherein the muscle derive cells are genetically engineered to express IGF-1, iNOS or IRAP polypeptides.

The state of the art at the time of filing teaches that stress urinary incontinence (SUI) occurs when urethral sphincter muscle is not sufficiently strong to prevent urine leakage for example while coughing or jumping (Chancellor et al, TRENDS in Mol. Med. 7(7):301-306, 2001; see Spec. page 8, lines 15-28). SUI is associated most often with pelvic floor muscle laxity. Weakened and streached out muscles and connective tissues lead to reduced muscle tension in the sphincter complex that's isufficient to keep the urethra closed tightly when pressure increases. Furthermore, in many patients the urinary incontinence is the result of mixed urge and stress incontinence (Newman et al Am J Nurs. 103(8):46-55, 2003, pages 48-51). The uretheral afferent nerve activity affects the micturition reflexes, indicating that in patients with stress urinary incontinence, the leakage of urine into proximal urethra stimulates afferent nerve, which facilitate voiding reflexes (Young et al, The Journal of Urology, 162:204-212, 1999, see abstract, conclusions). Furthermore detrusor weakness is a slowly progressing problem in human, whereas the murine-model as disclosed in the instant specification has only

shown physiological improvement following an acute cryo- induced injury. The state of the stress urinary incontinence art teaches that the graft success and the physiological improvement observed in the rodent-model may be absent in chronic weakness usually associated with humans (Huard et al Gene therapy 9:1617-1626, 2002 see page 1623 col.2). At best the instant specification disclosed injecting myoblasts (not U-MDCs) after 2, 4, and 7 days after urethral injury, which does not recapitulate conditions encompassing chronic stress urinary incontinence (spec page 55 lines 1-9). Therefore considering the unpredictability in the sate of stress urinary incontinence art and limited amount of guidance provided in the instant specification, it is highly unpredictable that the administering an undefined population of undifferentiated muscle derived cells *(autologous or allogenic; naïve or genetically modified)* would ameliorate injured, damaged or dysfunctional i) urethra muscle tissue, ii) sphincter muscle tissue iii) genitourinary tract tissue or iv) bladder tissue in the treatment of stress urinary incontinence.

Response to declaration

The applicant argues that the presently claimed invention sufficiently and effectively supports the repair of injured, damaged, or dysfunctional sphincter, bladder, or urethral muscle of the genitourinary tract following introduction of MDC into the relevant tissue. The applicant argues that Dr. Chancellor's declaration states that the cryo-induced injury to the urethra in rodents is an art-recognized and accepted animal model system to test and evaluate treatments and therapies for genitourinary tract disorders and dysfunctions. Applicant argues that assessment of leak point pressure (LPP) art-recognized parameter to assess MDC efficacy in the restoration of function and repair of urethral tissue. Increased LPP equates with increased continence and is an accepted parameter for assessing continence in clinical cases as well as in animal models of SUI. Accordingly the applicant concluded that Chancellor's declaration and experiments conducted in the cited references after the filing of the instant application, shows the beneficial effects of MDC for treating incontinence.

However, this is found not fully persuasive because the evidence provided the in the declaration is only limited to the amelioration of cryo-induced injury to the urethra

muscles in rodents, whereas the scope of invention as claimed encompasses repair and amelioration of an injury, damage or any dysfunction (motor or neurological) of urethra muscle tissue, sphincter muscle tissue, genitourinary tract tissue or bladder tissue. Furthermore, applicant argument that the administration of MDC would restores the function of injured, damaged or dysfunctional uro-genital tissues (as claimed) has been found not persuasive because scope of invention as claimed is not limited to engraftment of MDC but encompasses undifferentiated muscle derived cells. In contradiction to Chancellor's declaration the article published in the journal Gene Therapy 9:1617-25. 2002, *(where Dr. Chancellor is one of the author)* clearly states that the graft success and the physiological improvement observed in the murine-model may be absent in chronic weakness usually associated with stress urinary incontinence in humans *(supra).* At best the instant specification teaches the injection of genetically engineered GH8 myoblast cell line (not MDC as claimed) expressing β-galactosidase into the urethral wall of adult female rat with cryo-induced uretheral injury (page 54, example-2, table-1). The instant specification fails to provide any evidence that administration of an undefined population undifferentiated muscle-derived cells would treat stress urinary incontinence by repairing injured, damaged or dysfunctional i) urethra muscle tissue, ii) sphincter muscle tissue iii) genitourinary tract tissue or iv) bladder tissues. The specification fails to define what constitutes a population of undifferentiated muscle-derived cells. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case treatment of stress urinary incontinence by administering an undefined population of undifferentiated muscle-derived cells is not considered routine in the art and without sufficient guidance to a specific undifferentiated MDC cell type, along with therapeutic effects of IRAP, IGF-1 or iNOS and etiology of urinary incontinence in a particular type SUI, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claims 196-259 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "undifferentiated muscle derived cells (MDCs)" is a relative term, which renders the claim indefinite. The term "muscle derived cell" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably ascertain of the scope of the invention. In addition muscle cells are considered differentiated cells and it is unclear how one skill in the art would derive undifferentiated cells from a differentiated cell population. Furthermore, it is unclear what constitutes a non-adherent, non-fibroblast, desmin-positive cell this context, since desmin is known to express in all muscle cell types. The instant claims fails to define what are the phenotypic or genotypic characteristics of undifferentiated MDC.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S.Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER